

APPENDIX B

APPLICATION OF THE TARARA CLAIMS
TO THE DISCLOSURE OF THE TARARA APPLICATIONS

The Tarara Applications referred to in this Appendix B are U.S. Serial No. 09/886,296, the parent of this application and U.S. Serial No. 60/060,337 ('337). Disclosure from '337 is in parenthesis.

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Tarara Claims	Tarara Disclosure
<p>2. A composition comprising microspheres,</p> <p>wherein said microspheres have a wall thickness of 100 to 500 nm,</p> <p>and a bulk density of no more than 0.1 g/cm³</p>	<p>As to the configuration, particularly preferred embodiments of the invention incorporate spray dried, hollow microspheres having a relatively thin porous wall defining a large internal void, although other void containing or perforated structures are contemplated as well. (p. 6, l. 7-12)</p> <p>In especially preferred embodiments the perforated microstructures will comprise a powder of dry, hollow, porous microspherical shells of approximately 1 to 10 μm or 1 to 5 μm in diameter, with a shell thickness of approximately 0.1 μm to approximately 0.5 μm. (p. 32, l. 21-23)</p> <p>('337: Pg. 29, Lines 2-5 The process may be used to form a powder of dry hollow, approximately microspherical porous shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.2 μm.)</p> <p>Compositions according to the present invention typically yield powders with bulk densities less than 0.5 g/cm³ or 0.3 g/cm³, preferably less than 0.1 g/cm³ and most preferably less than 0.05 g/cm³. (p. 12, l. 26-28)</p> <p>('337: Pg. 42, Line 29 to Pg. 43, Line 17 Example II Particles with diameters of 1 μm to 15 μm were produced. Using the weighted density of the shell materials and a wall thickness of 0.2 μm, particles with 15 μm diameter would have a density of about 0.1 g/cm³)</p>

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3. The composition according to claim 2, wherein the mean geometric particle size of said microspheres is less than 20 μm .	<p>In especially preferred embodiments the mean geometric particle size (or diameter) of the perforated microstructures is less than 20 μm or less than 10 μm. (p. 32, l. 16-17)</p> <p>('337: Pg. 23, Lines 15-18 More preferably the average diameter of the dispersed microstructures is from about 0.5 μm to about 20 μm and even more preferably from about 1 μm to about 10 μm.)</p>
4. The composition according to claim 2, wherein the wall thickness of said microspheres is from 43.5 to 261 nm.	<p>Conversely, the perforated microstructures produced using a relatively high PFC/PC ratio of approximately 45 (shown in Fig. 1F2 proved to be extremely hollow with a relatively thin wall ranging from about 43.5 to 261 nm. (p. 65, l. 3-6)</p> <p>('337: Pg. 29, Lines 2-5 The process may be used to form a powder of dry hollow, approximately microspherical porous shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.2 μm.)</p>

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<p>5. The composition according to claim 2 wherein the walls of said microspheres comprise albumin.</p>	<p>In this respect useful polymers comprise polylactides, polylactide-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.). (p. 16, l. 22-25)</p> <p>('337: Pg. 25, Lines 8-14 In this respect useful polymers comprise polylactides, polylactideglycosides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), proteins, (albumin, collagen, gelatin, etc.).)</p>
<p>6. The composition according to claim 2 obtainable by spray-drying a wall-forming material in combination with a blowing agent</p>	<p>As previously described, these blowing agents will preferably be incorporated in an emulsified feed stock prior to spray drying. (p. 24, l. 1-2)</p> <p>('337: Pg. 31, Lines 26-28 The inclusion of an inflating agent in the solution to be spray-dried results in the formation of a greater number of hollow microspheres.)</p>

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<p>7. The composition according to claim 2 wherein said microspheres comprise a bioactive agent.</p>	<p>As used herein, the term "bioactive agent" refers to a substance which is used in connection with an application that is therapeutic or diagnostic in nature, such as methods for diagnosing the presence or absence of a disease in a patient and/or methods for treating disease in a patient (p. 8, l. 27-30)</p> <p>It will be appreciated that the perforated microstructures of the present invention may exclusively comprise one or more active or bioactive agents (i.e. 100% w/w). However, in selected embodiments the perforated microstructures may incorporate much less bioactive agent depending on the activity thereof. (p. 18, l. 17-20)</p> <p>('337: Pg. 34, Lines 27-31 Particularly preferred bioactive agents for use in accordance with the invention include anti-allergics, bronchodilators and anti-inflammatory steroids for use in the treatment of respiratory disorders such as asthma by inhalation therapy)</p>

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8. The composition according to claim 7, wherein said microspheres comprise a protein or peptide.	<p>Compatible bioactive agents comprise hydrophilic and lipophilic respiratory agents, pulmonary surfactants, bronchodilators, antibiotics, antivirals, anti-inflammatories, steroids, antihistaminics, leukotriene inhibitors or antagonists, anticholinergics, antineoplastics, anesthetics, enzymes, cardiovascular agents, genetic material including DNA and RNA, viral vectors, immunoactive agents, imaging agents, vaccines immunosuppressive agents, peptides, proteins and combinations thereof. (p. 19, l. 8-13)</p> <p>('337: Pg. 35, Line 13 to Page 36, Line 3 Preferred bioactive agents comprise hydrophilic and lipophilic respiratory agents, bronchodilators, bronchoconstrictors, antibiotics, antivirals, mydriatics, anti-inflammatories, antihistaminics, antineoplastics, anesthetics, ophthalmic agents, enzymes, cardiovascular agents, genetic material including DNA and RNA, viral vectors, immunoactive agents, imaging agents, immunosuppressive agents, peptides, proteins and combinations thereof.)</p>

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<p>9. The composition according to claim 7, wherein said microspheres comprise an active agent selected from the group consisting of insulin, growth hormone and interferon.</p>	<p>More specifically, exemplary medicaments or bioactive agents may be selected from, for example,... therapeutic proteins and peptides, e.g. DNase, insulin, glucagon; LHRH, nafarelin, goserlin, leuprolide, interferon, rhu IL-1 receptor, macrophage activation factors such as lymphokines and muramyl dipeptides, opioid peptides and neuropeptides such as enkaphalins, endorphins, renin inhibitors, cholecystokinins, DNase, growth hormones leukotriene inhibitors and the like. (p. 19, l. 17 to p. 20, l. 1)</p> <p>('337: Pg. 52, Line 19 to Page 53, Line 28 Example XVI Preparation of Perforated Microstructure Powder Containing Insulin)</p>

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<p>10. An inhaler comprising an inhalable formulation of microspheres</p> <p>wherein said microspheres have</p> <p>a wall thickness of 100 to 500 nm,</p> <p>and a bulk density of no more than 0.1 g/cm³</p> <p>and wherein said microspheres comprise a bioactive agent.</p>	<p>The perforated microstructures will preferably be used in conjunction with inhalation devices such as a metered dose inhaler, dry powder inhaler or nebulizer for both topical and systemic delivery via pulmonary or nasal routes. (p. 1, l. 15-19)</p> <p>See claim 2 above.</p> <p>It will be appreciated that the perforated microstructures of the present invention may exclusively comprise one or more active or bioactive agents (i.e. 100% w/w). However, in selected embodiments the perforated microstructures may incorporate much less bioactive agent depending on the activity thereof. (p. 18, l. 17-20)</p> <p>('337: Pg. 40, lines 30-33 Each filled cannister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient.)</p>
<p>11. The inhaler according to claim 10, wherein the formulation comprises the microspheres as the sole or the predominant component thereof.</p>	<p>In this respect the present invention provides formulations wherein the medicament and the excipients or bulking agents are preferably associated with or comprise the perforated microstructures...Moreover, the ability to effectively deliver particulates without associated carrier particles simplifies product formulation, filling and reduces undesirable side effects. (p. 42, l. 15-26)</p>

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<p>12. A method for pulmonary administration of a bioactive agent wherein said method comprises the administration to the lungs of</p> <p>a composition which comprises microspheres having a wall thickness of 100 to 500 nm and a bulk density of no more than 0.1 g/cm³, wherein said microspheres further comprise a bioactive agent.</p>	<p>More particularly, the present invention may provide for the delivery of bioactive agents to selected physiological target sites using perforated microstructure powders. In preferred embodiments, the bioactive agents are in a form for administration to at least a portion of the pulmonary air passages of a patient in need thereof. (p. 4, l. 27-31)</p> <p>('337: Pg. 7, Lines 24-27 As indicated above, the dispersions of the present invention are particularly compatible with inhalation therapies comprising administration of the bioactive preparation to the lung.)</p> <p>See claims 2 and 10 above.</p>
<p>13. The method according to claim 12, wherein the mean geometric diameter of said microspheres is less than 20 μm.</p>	<p>In especially preferred embodiments the mean geometric particle size (or diameter) of the perforated microstructures is less than 20 μm or less than 10 μm. (p. 32, l. 16-17)</p> <p>('337: Pg. 23, Lines 15-18 More preferably the average diameter of the dispersed microstructures is from about 0.5 μm to about 20 μm and even more preferably from about 1 μm to about 10 μm.)</p>

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<p>14. The method according to claim 12, wherein the wall thickness of said microspheres is from 43.5 to 261 nm.</p>	<p>Conversely, the perforated microstructures produced using a relatively high PFC/PC ratio of approximately 45 (shown in Fig. 1F2 proved to be extremely hollow with a relatively thin wall ranging from about 43.5 to 261 nm. (p. 65, l. 3-6)</p> <p>('337: Pg. 29, Lines 2-5 The process may be used to form a powder of dry hollow, approximately microspherical porous shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.2 μm.)</p>
<p>15. The method according to claim 12, wherein the walls of said microspheres comprise albumin.</p>	<p>In this respect useful polymers comprise polylactides, polylactide-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.). (p. 16, l. 22-25)</p> <p>('337: Pg. 25, Lines 8-14 In this respect useful polymers comprise polylactides, polylactideglycosides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), proteins, (albumin, collagen, gelatin, etc.).)</p>

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<p>16. The method according to claim 12, wherein said microspheres are obtainable by spray-drying a wall-forming material, in combination with a blowing agent.</p>	<p>As previously described, these blowing agents will preferably be incorporated in an emulsified feed stock prior to spray drying. (p. 24, l. 1-2)</p> <p>('337: Pg. 31, Lines 26-28 The inclusion of an inflating agent in the solution to be spray-dried results in the formation of a greater number of hollow microspheres.)</p>
<p>17. The method according to claim 12, wherein said microspheres comprise a protein or peptide.</p>	<p>Compatible bioactive agents comprise hydrophilic and lipophilic respiratory agents, pulmonary surfactants, bronchodilators, antibiotics, antivirals, anti-inflammatories, steroids, antihistaminics, leukotriene inhibitors or antagonists, anticholinergics, antineoplastics, anesthetics, enzymes, cardiovascular agents, genetic material including DNA and RNA, viral vectors, immunoactive agents, imaging agents, vaccines immunosuppressive agents, peptides, proteins and combinations thereof. (p. 19, l. 8-13)</p> <p>('337: Pg. 35, Line 13 to Page 36, Line 3 Preferred bioactive agents comprise hydrophilic and lipophilic respiratory agents, bronchodilators, bronchoconstrictors, antibiotics, antivirals, mydriatics, anti-inflammatories, antihistaminics, antineoplastics, anesthetics, ophthalmic agents, enzymes, cardiovascular agents, genetic material including DNA and RNA, viral vectors, immunoactive agents, imaging agents, immunosuppressive agents, peptides, proteins and combinations thereof.)</p>

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<p>18. The method according to claim 12, wherein said microspheres contain a bioactive agent selected from the group consisting of insulin, growth hormone and interferon.</p>	<p>More specifically, exemplary medicaments or bioactive agents may be selected from, for example, ... therapeutic proteins and peptides, e.g. DNase, insulin, glucagon, LHRH, nafarelin, goserlin, leuprolide, interferon, rhu IL-1 receptor, macrophage activation factors such as lymphokines and muramyl dipeptides, opioid peptides and neuropeptides such as enkaphalins, endorphins, renin inhibitors, cholecystokinins, DNase, growth hormones leukotriene inhibitors and the like. (p. 19, l. 17 to p. 20, l. 1)</p> <p>('337: Pg. 52, Line 19 to Page 53, Line 28 Example XVI Preparation of Perforated Microstructure Powder Containing Insulin)</p>
<p>19. A method for diagnosis wherein said method comprises administering to a patient in need of such diagnosis,</p>	<p>As used herein, the terms "bioactive agent" refers to a substance which is used in connection with an application that is therapeutic or diagnostic in nature, such as methods for diagnosing the presence or absence of a disease in a patient and/or methods for treating disease in a patient. (p. 8, l. 27-30)</p> <p>('337: Pg. 34, lines 22-27 As used herein, the terms "bioactive agent" refers to a substance which is used in connection with an application that is therapeutic or diagnostic in nature, such as methods for diagnosing the presence or absence of a disease in a patient and/or methods for treating disease in a patient.)</p>
<p>a composition which comprises microspheres having a wall thickness of 100 to 500 nm and a bulk density of no more than 0.1 g/cm³.</p>	<p>See claim 2 above.</p>

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20. The method according to claim 19, wherein the mean geometric diameter of said microspheres is less than 20 μm .	<p>In especially preferred embodiments the mean geometric particle size (or diameter) of the perforated microstructures is less than 20 μm or less than 10 μm. (p. 32, l. 16-17)</p> <p>('337: Pg. 23, Lines 15-18 More preferably the average diameter of the dispersed microstructures is from about 0.5 μm to about 20 μm and even more preferably from about 1 μm to about 10 μm.)</p>
21. The method according to claim 19, wherein the wall thickness of said microspheres is from 43.5 to 261 nm.	<p>Conversely, the perforated microstructures produced using a relatively high PFC/PC ratio of approximately 45 (shown in Fig. 1F2 proved to be extremely hollow with a relatively thin wall ranging from about 43.5 to 261 nm. (p. 65, l. 3-6)</p> <p>('337: Pg. 29, Lines 2-5 The process may be used to form a powder of dry hollow, approximately microspherical porous shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.2 μm.)</p>

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<p>22. The method according to claim 19, wherein the walls of said microspheres comprise albumin.</p>	<p>In this respect useful polymers comprise polylactide, polylactide-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.). (p. 16, l. 22-25)</p> <p>('337: Pg. 25, Lines 8-14 In this respect useful polymers comprise polylactides, polylactideglycosides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), proteins, (albumin, collagen, gelatin, etc.).)</p>
<p>23. The method according to claim 19, wherein said microspheres are obtainable by spray-drying a wall-forming material, in combination with a blowing agent.</p>	<p>As previously described, these blowing agents will preferably be incorporated in an emulsified feed stock prior to spray drying. (p. 24, l. 1-2)</p> <p>('337: Pg. 31, Lines 26-28 The inclusion of an inflating agent in the solution to be spray-dried results in the formation of a greater number of hollow microspheres.)</p>

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<p>24. A method for preparing microparticles, wherein said method comprises spray-drying wall-forming materials and wherein said method further comprises inclusion of a blowing agent in the feedstock for spray-drying.</p>	<p>While the resulting spray-dried powdered particles typically are approximately spherical in shape, nearly uniform in size and frequently are hollow, there may be some degree of irregularity in shape depending upon the incorporated medicament and the spray drying conditions. In many instances dispersion stability and dispersibility of the perforated microstructures appears to be improved if an inflating agent (or blowing agent) is used in their production. Particularly preferred embodiments may comprise an emulsion with the inflating agent as the disperse or continuous phase. (p. 22, l. 12-18)</p> <p>('337: Pg. 31, Lines 16-31 The inclusion of an inflating agent in the solution to be spray-dried results in the formation of a greater number of hollow microspheres. The inflating agent nucleates steam bubble formation within the atomized droplets of the solution entering the spray dryer as these droplets mix with the hot air from steam within the dryer.)</p>
<p>25. The method according to claim 24, wherein said blowing agent is selected from the group consisting of ammonium acetate, ammonium carbonate, and acids.</p>	<p>The inclusion of salts and organic solids such as ammonium carbonate, ammonium acetate, ammonium chloride or camphor is also contemplated. (p. 17, l. 22-23)</p> <p>('333: Pg.. 32, Lines 25-30 Other optional components may include conventional viscosity modifiers, buffers such as phosphate buffers or other conventional biocompatible buffers or pH adjusting agents such as acids or bases, and osmotic agents (to provide isotonicity, hyperosmolarity, or hyposomolarity).)</p>

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26. The method according to claim 24, wherein said wall-forming material is albumin	<p>In this respect useful polymers comprise polylactide, polylactide-glycolides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), hyaluronic acid, proteins, (albumin, collagen, gelatin, etc.). (p. 16, l. 22-25)</p> <p>('337: Pg. 25, Lines 8-14 In this respect useful polymers comprise polylactides, polylactideglycosides, cyclodextrins, polyacrylates, methylcellulose, carboxymethylcellulose, polyvinyl alcohols, polyanhydrides, polylactams, polyvinyl pyrrolidones, polysaccharides (dextrans, starches, chitin, chitosan, etc.), proteins, (albumin, collagen, gelatin, etc.).)</p>

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<p>27. A composition comprising microspheres,</p> <p>wherein said microspheres have a wall thickness of 100 to 500 nm,</p> <p>and a bulk density of no more than 0.3 g/cm³</p>	<p>As to the configuration, particularly preferred embodiments of the invention incorporate spray dried, hollow microspheres having a relatively thin porous wall defining a large internal void, although other void containing or perforated structures are contemplated as well. (p. 6, l. 7-12)</p> <p>In especially preferred embodiments the perforated microstructures will comprise a powder of dry, hollow, porous microspherical shells of approximately 1 to 10 μm or 1 to 5 μm in diameter, with a shell thickness of approximately 0.1 μm to approximately 0.5 μm. (p. 32, l. 21-23)</p> <p>('337: Pg. 29, Lines 2-5 The process may be used to form a powder of dry hollow, approximately microspherical porous shells of approximately 1 to 10 μm in diameter, with shell thicknesses of approximately 0.2 μm.)</p> <p>Compositions according to the present invention typically yield powders with bulk densities less than 0.5 g/cm³ or 0.3 g/cm³, preferably less than 0.1 g/cm³ and most preferably less than 0.05 g/cm³. (p. 12, l. 26-28)</p> <p>('337: Pg. 42, Line 29 to Pg. 43, Line 17 Example II Particles with diameters of 1 μm to 15 μm were produced. Using the weighted density of the shell materials and a wall thickness of 0.2 μm, particles with 15 μm diameter would have a density of about 0.1 g/cm³)</p>

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28. The composition according to claim 2 wherein the bulk density is no more than 0.05 g/cm ³ .	Compositions according to the present invention typically yield powders with bulk densities less than 0.5 g/cm ³ or 0.3 g/cm ³ , preferably less than 0.1 g/cm ³ and most preferably less than 0.05 g/cm ³ . (p. 12, l. 26-28)